**REMARKS**

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 93, 95 and 98-120 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 93, 95 and 98-120 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al., *Infect. Immun.* 61:64-70 (1993). This rejection is respectfully traversed.

In the previous response filed April 28, 2008, applicants stated that the factor disclosed in Nakamura is a mixture of a complex that comprises 44% of unpurified proteins other than the IGIF even if the factor comprises the IGIF disclosed in Okamura (*Infect. Immun.*, 63(10):3966-3972, 1995), and that it would have required undue experimentation to obtain the claimed monoclonal antibody using Nakamura's factor in such unpurified state.

The examiner, however, asserts that the applicants' arguments are not persuasive, stating that the applicants' calculation of 44% of unpurified proteins other than IGIF in Nakamura's factor is based on specific activity, and that Nakamura's factor can be considered to be a protein that is IGIF

but having lost 44% of its activity, and such protein has high purity.

The examiner's reasoning is respectfully traversed. It should be noted that the IGIF which lost its activity is a protein in which a part or the whole of the amino acid sequence and conformation of IGIF has been denatured. As such, it is clear that Nakamura's factor is an impure one which comprises at least 44% of denatured and inactive IGIF (i.e., which is not the IGIF but another one) other than the true and active IGIF. Applicants respectfully submit that Nakamura's factor is not same as the IGIF of Okamura.

As explained above, Nakamura's factor is a mixture or a complex which comprises 44% of proteins (denatured IGIF is included in the mixture or complex) other than the IGIF. Applicants respectfully submit that it would have been difficult to obtain a monoclonal antibody which recognizes IGIF using such an impure factor from Nakamura. In fact, Nakamura did not succeed in obtaining a monoclonal antibody against Nakamura's factor, even though Nakamura had need for such a monoclonal antibody more than anyone else.

Moreover, Nakamura states at page 69, left column, lines 8-12:

> However, details of the molecule such as its terminal amino acid sequence or amino acid composition to be compared with details of

> the known cytokines remain to be elucidated. We were unable to obtain sufficient amount of the factor for these purposes. (emphasis added)

This implies that Nakamura could not obtain a sufficient amount of the factor from the sera of mice to obtain a monoclonal antibody against the factor.

It is well known that a sufficient amount of antigen is needed to prepare monoclonal antibody using the antigen. For example, Okamura states at page 3972, left column, lines 12-15:

> The complementary DNA for the IGIF has recently been cloned (unpublished data). This will enable a sufficient supply of recombinant IGIF or the antibody against it for examination of its biological actions.

Since Okamura was published in 1995, which is two years later than Nakamura, the above cited statement indicates the fact that sufficient amount of IGIF to prepare a monoclonal antibody which recognizes the IGIF had not been available even two years after Nakamura's publication.

On the other hand, the Lochner et al., *Journal of Immunological Methods*, 259:149-157 (2002), reference submitted with the response of April 28, 2008, and made of record, discloses on page 150, left column, first full paragraph:

> Experimental inhibition of IL-18 function has been achieved through the use of neutralizing antibodies to IL-18 (Okamura et al., 1995; Tsutsui et al., 1997; Netea et al., 2000).

It is clear from this disclosure that antibodies to IL-18 or IGIF were prepared by using, not Nakamura's factor, but the IGIF or IL-18 of Okamura (1995), Tsutsui (1997), or Netea (2002).

It is also clear that a person of ordinary skill in the art could not have prepared a monoclonal antibody against IGIF or IL-18 using Nakamura's factor. This would be well recognized and understood by those of skill in the art because a protein with high purity is necessary in order to prepare a monoclonal antibody against the protein as antigen. In fact, the Sevier et al., *Clin. Chem.*, 27(11):1797-1806 (1981), reference submitted with the response of April 28, 2008, and made of record, discloses:

> To minimize screening problem when dealing with soluble antigens, the immunogen should be as pure as possible, because the purity of the immunogen may reflect the frequency of positive clones. (page 1798, left column, lines 2-6).

Furthermore, it should be indicated that Okamura states at page 3972, left column, liens 6-7:

> To solve this issue, a specific antibody, monoclonal if possible, will helpful. (emphasis added)

It is clear that even Okamura, who needed a monoclonal antibody against IGIF, did not obtain the monoclonal antibody in 1995, two years after Nakamura's publication. Applicants therefore submit that it would have been difficult even for a person skilled in

the art at the time Okamura was published in 1995 to prepare the monoclonal antibody.

Applicants note that the examiner cites the following statement in Okamura:

> Thus IGIF in the serum sample was proved to be the same as IGIF as found in liver extract.

This statement, however, only means that Nakamura's factor comprises Okamura's IGIF, but does not mean that Nakamura's factor was purified and isolated to the same level as Okamura's IGIF.

The examiner's attention is respectfully invited to the following statement in Nakamura:

> It is desirable also to examine B cells in murine systems, since the factor in the present study is induced by LPS and LPS is a strong stimulator for B cells. The apparent molecular weight of the active form of NSKF/IL-12; its IFN-γ inducibility; and the synergy with IL-2, anti-CD3 MAb, or a mitogenic lectin are all similar to those of the present factor. (page 69, left column, lines 22-28) (emphasis is added)

As shown above, Nakamura himself recognized that Nakamura's factor and MKSF/IL-12 were very similar in their physicochemical properties. Accordingly, neither Nakamura nor one of ordinary skill in the art were even aware of the presence of IGIF at the time Nakamura was published.

The examiner cites Boldain et al., *Monoclonal Antibodies for Cancer Detection And Therapy*, page 20 (1985), and states that it is relatively easy to make additional monoclonal antibodies to an antigen that has already been identified. However, this is not the case in the present application, because Nakamura did not identify IGIF. As such, it would have been difficult for one of ordinary skill in the art to make a monoclonal antibody which recognizes IGIF based on Nakamura's factor.

Furthermore, the examiner asserts that the technology for obtaining monoclonal antibodies was well established. However, the fact that the technology for obtaining monoclonal antibodies was well established does not mean that any monoclonal antibody could have been obtained with only routine experimentation at the time the present invention was made. The Sevier et al., *Clin. Chem.*, 27(11):1797-1806 (1981), reference discloses in the "Summary" section:

> … Hybridoma cell lines are easily generated, but selecting the proper clones and establishing them are quite different… (page 1802, left column, "Summary" section).

From this statement, it is clear to one of ordinary skill in the art that it would require undue experimentation to obtain the monoclonal antibody as claimed even though the technique for obtaining monoclonal antibodies was considered well established.

Applicants respectfully submit that it would have been difficult at the time the present invention was made to prepare various monoclonal antibodies using Nakamura's factor and the technique known to public, and to select a monoclonal antibody which recognizes IGIF (which was not identified by Nakamura). As mentioned above, Nakamura did not obtain any antibodies which recognize Nakamura's factor, much less a monoclonal antibody which recognizes IGIF. Furthermore, even Okamura, who published two years later than Nakamura, did not obtain antibodies which recognize the IGIF. Accordingly, Nakamura et al. cannot lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of this rejection are therefore respectfully solicited.

In view of the above, the claims define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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